# EXHIBIT K

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MEDLINE(R)

11832877 PMID: 9658317
Circulating vascular endothelial growth factor (VEGF) is a possible tumor marker for metastasis in human hepatocellular carcinoma.

Jinno K; Tanimizu M; Hyodo I; Nishikawa Y; Hosokawa Y; Doi T; Endo H; Yamashita T; Okada Y
Department of Clinical Research, National Shikoku Cancer Center Hospital, Matsuyama, Japan.
Journal of gastroenterology ( JAPAN ) Jun 1998 , 33 (3) p376-82 , ISSN: 0944-1174--Print Journal Code: 9430794
Publishing Model Print
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: MEDLINE; Completed
Vascular endothelial growth factor (VEGF) is closely related to angiogenesis in various human cancers. However, little is known of its circulating levels in hepatocellular carcinoma (HCC). We examined circulating VEGF levels in chronic liver disease to assess their clinical significance. Plasma VEGF concentrations were determined, by enzyme immunoassay, in patients with chronic hepatitis (CH; n = 36), liver cirrhosis (LC; n = 77), and HCC (n = 86) for a cross-sectional study. Plasma VEGF levels in healthy controls (n = 20) and CH, LC, and HCC patients were 17.7 +/- 5.4 (mean +/- SD), 30.6 +/- 22.8, 34.4 +/- 27.0, and 51.1 +/- 71.9 pg/ml, respectively. The levels were significantly elevated in the HCC group, compared with the control, CH, and LC groups. Plasma VEGF levels in stage I, II, III, IVA, and IVB HCC patients were 27.6 +/- 16.1, 26.5 +/- 13.7, 35.8 +/- 15.3, 45.4 +/- 39.4, and 103.1 +/- 123.2 pg/ml, respectively. The stage IVB patients with remote metastasis showed significantly marked elevation compared with the patients at the other stages. Platelet numbers were weakly correlated with plasma VEGF levels in the HCC group. Plasma VEGF level was highly elevated in patients with HCC, particularly those with metastatic disease. We consider that plasma VEGF is a possible tumor marker for metastasis of HCC. Circulating VEGF may be derived mainly from the large burden of tumor cells, and partly from platelets activated by the vascular invasion of HCC cells.